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## **vWF fibers induce thrombosis during cancer**

Borsig, Lubor

**Abstract:** In this issue of Blood, Bauer et al1 provide an explanation for the formation of luminal von Willebrand factor (vWF) fibers observed in cancer patients, which is initiated through tumor-derived VEGF-A. Platelet aggregation on vWF fibers correlated with a prothrombic state associated with decreased ADAMTS13 activity in cancer patients.

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that could undermine the therapeutic index of any one target. This target-rich environment, not restricted to mutated oncoproteins, offers real hope for breakthroughs (or at least improvements in safety and effectiveness) in MDS/AML therapy.

**Conflict-of-interest disclosure:** The author declares no competing financial interests. ■

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## ● ● ● THROMBOSIS AND HEMOSTASIS

Comment on Bauer et al, page 3153

# VWF fibers induce thrombosis during cancer

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In this issue of *Blood*, Bauer et al<sup>1</sup> provide an explanation for the formation of luminal von Willebrand factor (VWF) fibers observed in cancer patients, which is initiated through tumor-derived vascular endothelial growth factor-A (VEGF-A). Platelet aggregation on VWF fibers correlated with a prothrombotic state associated with decreased a disintegrin-like and metalloproteinase with thrombospondin type I repeats 13 (ADAMTS13) activity in cancer patients.

**T**he association between cancer and thromboembolism was first described by Trousseau more than 100 years ago, when he made the astute observation that patients with unexplained thrombosis sometimes had an occult malignancy.<sup>2</sup> The frequently observed prothrombotic state in cancer patients encompasses a broad variety of complications, ranging from thrombotic microangiopathy to deep vein thrombosis. The pathophysiology of cancer-associated thrombosis is rather complex, but can be linked to 3 major features: stasis, vascular injury, and hypercoagulability, according to the criteria of so-called Virchow triad.<sup>3</sup> Vascular alterations are frequently observed both in the primary tumor and at metastatic sites. Increased presence of VWF in the circulation correlates with endothelial

damage and is used as an indicator for many pathological situations, including atherosclerosis, cardiovascular disease, and cancer.<sup>4</sup> VWF forms polymer fibers attached to the luminal endothelial cells that contribute to hemostasis-mediating platelet adhesion. This process is normally controlled by the plasma metalloproteinase ADAMTS13.<sup>4</sup> However, VWF fibers also promote platelet aggregation, which may result in pathophysiological thrombi formation and vessel occlusion.<sup>5</sup> In the current work, Bauer et al<sup>1</sup> show that VWF fiber formation and the associated platelet aggregation is detected both in primary tumors of melanoma patients and in a mouse melanoma model. Although a clear increase in VWF fiber formation was detected in melanoma patients, there was

a small but significant decrease in ADAMTS13 in the tumors. However, enhanced VWF fiber formation in mouse melanoma tumors was associated with a clearly reduced ADAMTS13 activity. Consequently, intravenous infusion of recombinant ADAMTS13 significantly reduced luminal fiber formation in mouse tumors.

What causes endothelial damage during cancer progression that results in enhanced thromboembolism is still heavily debated. It is well known that a variety of procoagulant factors secreted by tumors such as tissue factor, thrombin, VEGF, mucins with selectin binding sites, or tumor necrosis factor has been shown to be abnormally raised during cancer and is linked to a prothrombotic state in patients.<sup>2,3,6</sup> In addition, these factors have been shown to trigger thrombosis in a variety of animal cancer models. In particular, VEGF is the primary factor inducing angiogenesis and therefore both physiological and pathophysiological activation of the endothelium. Previously, thrombin release by melanoma cells was shown to induce endothelial activation associated with VWF deposition in the vascular lumen.<sup>7</sup> Bauer et al now provide evidence that tumor-derived VEGF causes endothelial activation, resulting in enhanced VWF fiber deposits in the vasculature and thereby inducing platelet aggregation and thrombosis.

There is abundant literature on the use of heparin and low-molecular-weight derivatives (LMWH) in cancer patients. However, there is accumulating evidence that heparins have cancer inhibitory activity that goes beyond just anticoagulation.<sup>8</sup> Although a rigorous evaluation of heparin or LMWH on inhibition of cancer progression is still missing, virtually all animal models confirmed beneficial effects of heparin or LMWH on cancer progression.<sup>9,10</sup> Because of the complex biological nature of heparins, they can affect several potential mechanisms involved in metastasis, including cell adhesion through selectins, enzymatic activity of heparanase, or the activity of growth factors and cytokines. The study by Bauer et al<sup>1</sup> now provides evidence that LMWH tinzaparin directly binds to VEGF and thereby reduces melanoma-induced endothelial activation associated with VWF fiber formation. These findings show yet another mechanism for how heparins may interfere with endothelial activation and angiogenesis. Long-term tinzaparin treatment of transgenic mice,

which spontaneously develop skin melanomas, significantly prolonged survival in these mice. In particular, reduced VEGF amounts in tumors and reduced tumor cell proliferation were affected by tinzaparin treatment, which likely reflect a reduced angiogenesis and cancer progression.

Taken together, the work of Bauer et al<sup>1</sup> provides an important contribution to our understanding of cancer-induced prothrombotic activity with regard to endothelial activation and VWF fiber formation in the lumen of cancer-associated vasculature. Although this work convincingly shows the relevance of VWF fibers formation and associated platelet aggregation in primary tumors of cancer patients, the fundamental question as whether VWF fiber formation occurs during metastatic initiation requires further investigation. Along these lines, the current findings show that endothelial activation is a critical requirement for successful metastasis. A better understanding of molecular events leading to VWF fiber deposition and subsequent microthrombus formation could allow the designing of new therapy approaches.

**Conflict-of-interest disclosure:** The author declares no competing financial interests. ■

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## ● ● ● THROMBOSIS AND HEMOSTASIS

Comment on Prakash et al, page 3164

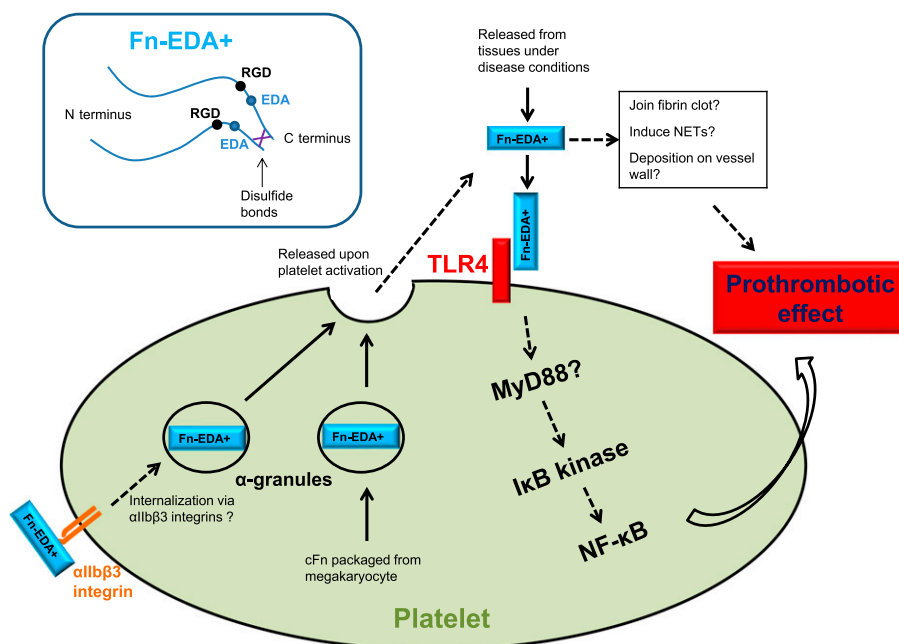
# Fibronectin: extra domain brings extra risk?

Yiming Wang<sup>1,2</sup> and Heyu Ni<sup>1,2</sup> <sup>1</sup>ST. MICHAEL'S HOSPITAL; <sup>2</sup>CANADIAN BLOOD SERVICES

In this issue of *Blood*, Prakash et al provide compelling *in vitro* and *in vivo* evidence for a novel role of cellular fibronectin (cFn) containing extra domain A (Fn-EDA+) in arterial thrombosis.<sup>1</sup>

**F**ibronectins (Fn's) are large dimeric multidomain glycoproteins consisting of two 230- to 250-kDa monomers linked by disulfide bonds at their C terminus. Each Fn monomer contains collagen and fibrin binding sites in the N terminus and an Arg-Gly-Asp (RGD) integrin binding motif. The alternative splicing of Fn pre-messenger RNA (pre-mRNA) generates several Fn variants, which can be grouped into 2 main categories: plasma fibronectin (pFn) and cFn. In contrast to pFn, cFn contains either EDA or EDB or both.<sup>2</sup> Fn's are widely distributed in extracellular matrix and blood circulation. They are required for embryogenesis, and are important for wound healing, infection, and malignant transformation.<sup>3</sup>

Using intravital microscopy models, the roles of both pFn and cFn in thrombosis have been established in the past decade.<sup>4-7</sup> pFn is synthesized in the hepatocytes and accounts for almost all of the Fn's in the normal blood plasma. The depletion of pFn in mice resulted in a decrease of thrombus growth and stability.<sup>4</sup> It was later found that pFn supports platelet aggregation and thrombosis only in the presence of fibrin, and the pFn-fibrin complex may be a prerequisite for its prothrombotic activities.<sup>5,6</sup> In the absence of fibrin (eg, at the apical surface of the growing thrombi), pFn inhibits platelet aggregation, thus preventing excessive thrombosis and rescuing downstream blood supply.<sup>6</sup> pFn also supports hemostasis through depositing on the injured vessel wall



Fn-EDA+ interacts with platelet TLR4 to promote thrombosis, possibly through the platelet NF- $\kappa$ B signaling pathway. Platelet intracellular Fn-EDA+ is packaged from megakaryocytes and possibly also internalized via  $\alpha$ IIb $\beta$ 3 integrins, which are released upon activation from platelet  $\alpha$ -granules. Fn-EDA+ may incorporate into fibrin clots, deposit on vessel wall, and induce NET formation.



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